154. An Electrochemical Variant in the Syntheses of Exaltone® and Muscone: Anodic Fragmentation of α,β-Unsaturated Tosylhydrazones

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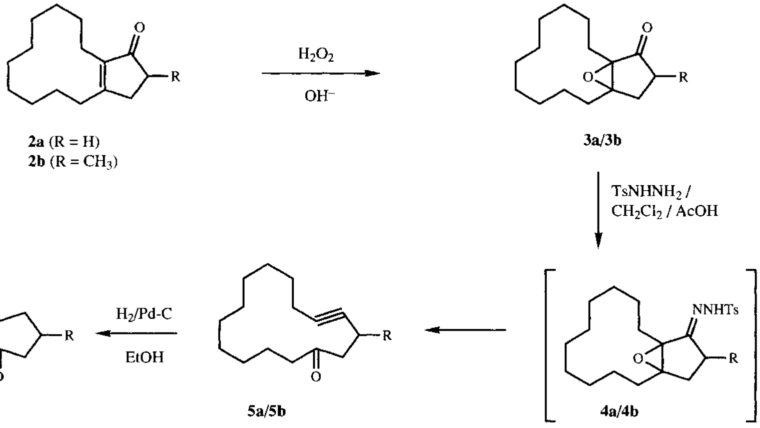
Dedicated to Dr. *Günther Ohloff* on the occasion of his 65th birthday

(25.V.89)

Ring enlargement of bicyclo[10.3.0]pentadec-1(12)-en-13-one p-toluenesulfonylhydrazone into cyclopentadec-4-yn-1-one was accomplished under mild and controlled anodic oxidation conditions. The mechanism of this fragmentation is reconsidered.

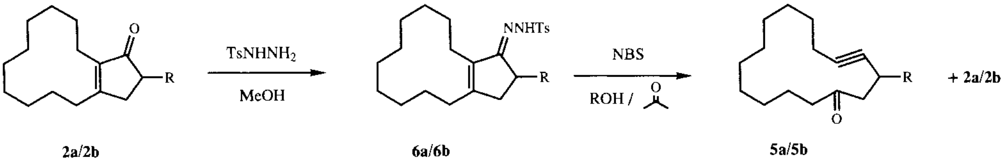
Introduction. – Among the numerous routes to Exaltone® (**1a**) and muscone (**1b**), which belong to the class of macrocyclic musk odorants, the three-C-atom ring enlargement of readily available cyclododecane derivatives has been widely exploited. Particularly elegant was the strategy involving fragmentation of the bicyclic α,β-epoxy-ketones **3** into the monocyclic γ-ynones **5** [1] (*Scheme 1*).

Scheme 1



However, the difficulties encountered in the epoxidation steps (yields of 60% and 0% for **3a** and **3b**, respectively) led subsequently to pertinent modifications [2][3]. They consisted mainly in inversing the oxidation (**2** → **3**) and the hydrazone-forming (**3** → **4**) steps (*Scheme 2*). Oxidations of the intermediate tosylhydrazones **6** have been performed by

Scheme 2



means of either hypochlorites or *N*-bromoimides with a hydroxylic solvent as nucleophile at low temperatures. Interestingly enough, the desired 1,4-nucleophilic attack on the masked enone could be markedly favoured over the 1,2-process.

In view of the interest in Exaltone® (**1a**) and muscone (**1b**) as ingredients in perfumery, it was worth to investigate this fragmentation, in particular to test other oxidation techniques. Among them, an anodic electrode process, which would allow an easy control of the reaction rate, proved to be very attractive.

Results. – Electrolyses were conducted in 5% solutions of the tosylhydrazone **6a** (or **6b**) in MeOH/MeCN 7:3 containing 0.1M of a tetraalkylammonium salt as supporting electrolyte. According to previous mechanistic assumptions [4], MeOH (or another aliphatic alcohol) was necessary as nucleophile, and MeCN was added to increase the solubility of the hydrazones. Graphite or Pt could be used as anodes, while the choice of the cathode material was not crucial and could be extended to any metal or alloy of low hydrogen overpotential (Pt, Ti, Ni, Cu, Monel, stainless steel, *etc.*; Hg, Pb, Zn, and graphite proved unsuitable), reduction of MeOH being the second half-cell reaction. An undivided cell configuration was chosen upon examination of the cyclic voltammogram, which exhibited a single apparent two-electron irreversible wave during anodic potential sweeps [5]. A peak potential of 1.2 V (*vs.* saturated calomel electrode) has been measured at the steady state (10 cycles) on a vitreous carbon electrode[1]) (*Fig. 1*).

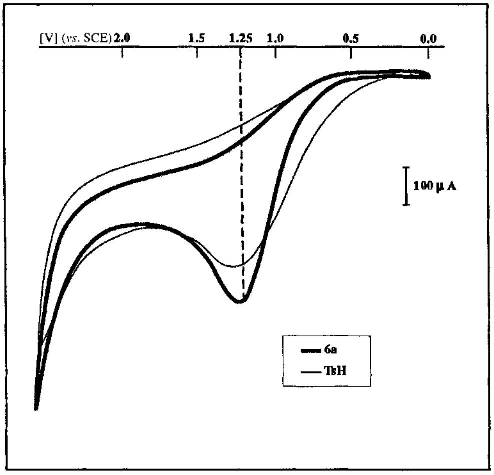


Fig. 1. *Cyclic voltammograms of* **6a** *and* p-*toluenesulfinic acid*

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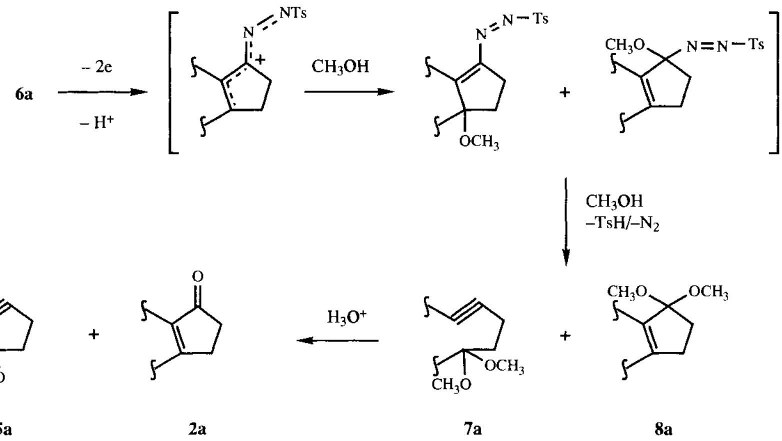
[1]) GC-A Grade, Code *EB-3* purchased from *IMC Industry Group Associates Inc.*, Japan.

Referring again to the postulated mechanism [3] (*Scheme 3*), the oxidized hydrazones **6** led to two intermediate acetals **7** and **8**, which under aqueous workup conditions, afforded ketones **5** and **2**, respectively. The fragmentation process itself, therefore, liberates 1 equiv. of *p*-toluenesulfinic acid (TsH), which, in its turn, is oxidized at a very similar potential (*Fig. 1*). In fact, TsH[2]) was shown to undergo a two-electron oxidation under the fragmentation conditions to give TsOMe. Consequently, the theoretical quantity of electricity required for the overall fragmentation process amounts to 4 F/mol.

Scheme 3



The choice of the electrolyte was restricted to a tetraalkylammonium salt for solubility reasons. The course of the reaction was totally unaffected by the nature of the alkyl residue (C(1) to C(4)) of the ammonium moiety. *Fig. 2* shows, however, a close dependence of yields and product ratios on the anion.

At room temperature and a current density of 50 mA/cm^2, the fragmentation of either hydrazone **6a** or **6b** led to 80% yield of a 65:35 mixture of ynone **5a** or **5b** and enone **2a** or **2b** after consumption of 4 F/mol electricity. In fact, the true product distribution seemed to approximate 1:1 and to be fairly insensitive to variations of temperature (10–60°) or current density (5–100 mA/cm^2). However, especially at high temperatures and high current densities, enones **2** were less stable than ynones **5**.

In an attempt to further examine the hydrolysis step, we tried to isolate acetals **7a** and **8a** prior to the usual aqueous workup. To our surprise, we obtained the monocyclic acetal **7a** and ketone **2a**, but no trace of acetal **8a**. Repeating the electrolysis experiment under strictly anhydrous conditions confirmed the exclusive formation of **7a** and **2a** in a 2:1 ratio. Quite unexpected too was the observation of the concomitant formation of TsOMe and TsMe in the same 2:1 ratio. Monitoring the reaction by GLC showed that the product distribution (*Scheme 4*) remained time-independent.

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[2]) The unstable free *p*-toluenesulfinic acid [6] has been prepared *in situ* by acidification of its commercially available Na salt.

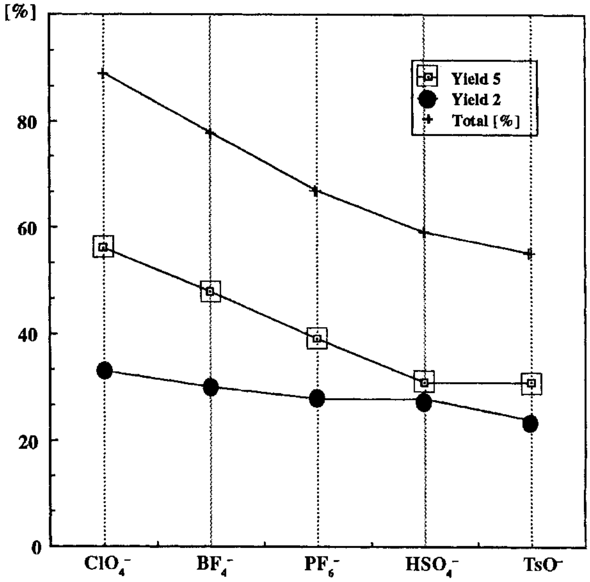
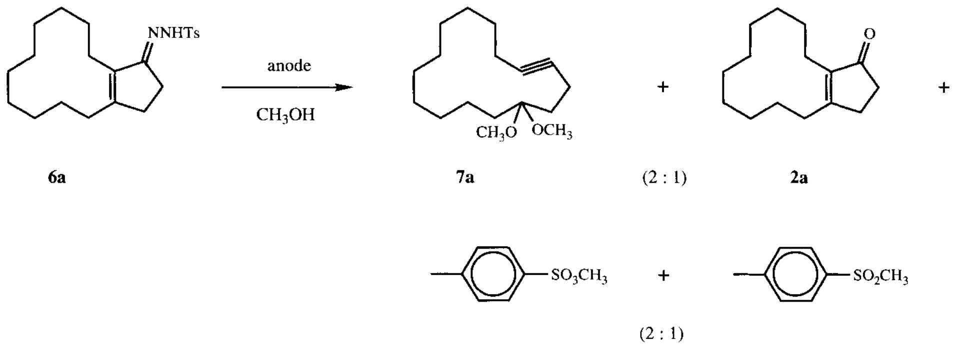


Fig. 2. *Influence of the electrolyte anion on the yields*

Scheme 4

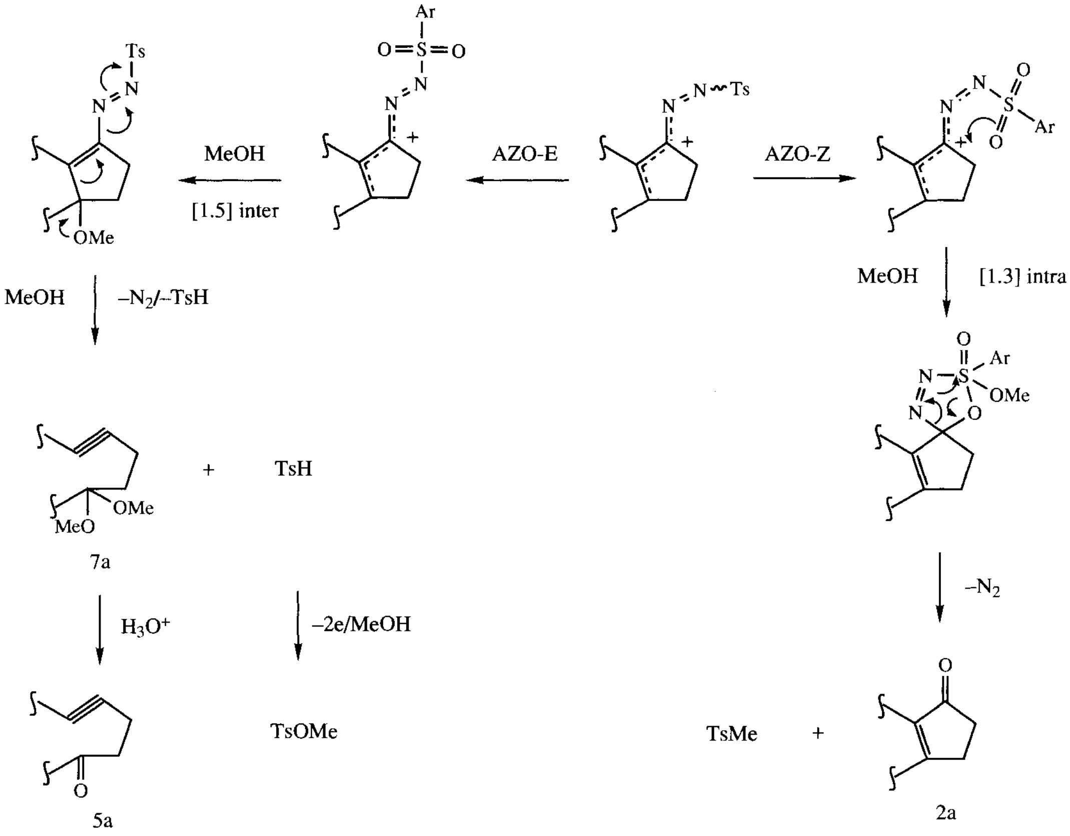


Hydrolysis of the crude electrolysis solution with 1% (*v:v*) of 0.1% aq. H_2SO_4 at room temperature quantitatively converted **7a** into **5a**, leaving **2a** unaffected. The presence in the reaction mixture of a substantial amount of TsMe, a non-oxidized form of the leaving TsH, prompted us to re-evaluate the amount of electricity required for the entire fragmentation process. Indeed, coulometry experiments indicated reproducible energy consumptions of 3.2–3.4 F/mol, but never 4 F/mol. The initial mechanism, which was believed to operate up to now, had, thus, to be reconsidered.

Discussion. – Strong evidence against full acceptation of the mechanism so far invoked for this fragmentation (*Scheme 3*) emerges from these results. They suggest the occurrence of two separate and well-defined pathways each leading to one single product. Clearly, the O-atoms in the C=O functions of **2** and **5** do *not* have their origin in a common intermediate. A plausible hypothesis, which closely fits all experimental facts, is outlined in *Scheme 5*.

The first intermediate of the oxidation step is a azopentenyl-cation moiety, and it is not unreasonable to consider it as a mixture of two interconvertible geometrical isomers with respect to the N=N bond, which we have called *AZO-E* and *AZO-Z*. Assuming that C(3) of these delocalized cations is sterically crowded, it follows that the *AZO-E* species can only undergo an intermolecular 1,5-addition of MeOH and leads, as expected, to the fragmented acetal **7** and TsH. The latter then undergoes a two-electron oxidation in the presence of MeOH to give TsOMe. In contrast, *AZO-Z* favours an intramolecular participation of the neighbouring sulfonyl group with the assistance, concerted or not, of MeOH on the S-atom to generate a spirocyclic entity, which most likely falls apart spontaneously to give enone **2**, N_2, and TsMe [7].

Scheme 5



This interpretation accounts well for the identified structures, their relative ratio in the reaction mixture, and the stoichiometry of electricity, the calculated value of 3.3 F/mol being now in fair agreement with the experimental one (3.2–3.4 F/mol).

The factors controlling the ynone-**5**-to-enone-**2** ratio still remain unclear: does the steric bulkiness of the leaving sulfonyl group play a significant role in this mechanistic dichotomy? A partial positive answer was provided by oxidation of the corresponding, less crowded mesylhydrazone of **2a**[3]), which indeed led to predominant formation of enone **2a** (77%) over ynone **5a** (23%). Experiments with bulkier arylsulfonylhydrazones are under study to corroborate this assumption.

We are indebted to Prof. *A. Eschenmoser* for stimulating discussions and fruitful suggestions.

Experimental Part

General. Workup refers to: washing of the combined org. phases with H_2O and aq. sat. NaCl soln., drying (Na_2SO_4), filtration, and evaporation of the solvent. GLC was performed on a model *2450 Carlo Erba* instrument, using *5% SE-30* or *5% Carbowax 20M* as liquid phases on *Chromosorb W* (80-100 mesh ASTM, acid-washed and silanized). B. p. uncorrected. IR spectra: as films or CCl_4 solns. on a *Perkin-Elmer A-21* spectrophotometer (max. in cm^{-1}). ^1H-NMR spectra ($CDCl_3$): *Bruker WH-360* instrument. Chemical shifts (δ) are given in ppm downfield from TMS. Coupling constants *J* are in Hz. MS: on a *Finnigan* quadrupole instrument coupled with a GC and reported in *m/z* (% most important fragment).

Cyclic voltammograms were recorded using combined model *552* potentiostat and model *563* function generator *AMEL* instruments at 0.15M concentration of the substrate on vitreous carbon (0.16 cm^2)[1]) *vs.* sat. calomel electrode (SCE, with a 3M aq. LiCl bridge junction) at a sweep rate of 100 mV/s.

Preparative electrolyses were performed in a magnetically stirred three-necked 100-ml flask as single compartment cell, fitted with a condenser connected to a N_2 line, a thermometer, and a *Teflon* stopper bearing a graphite anode (3 x 2 cm^2)[4]) and a stainless steel cathode (3 x 2 cm^2) 10 mm apart, using a model *550* (100 W) *AMEL* potentiostat.

Anodic Oxidations. General Procedure. A soln. of **6a** (or **6b**; 0.013 mol) and Bu_4NClO_4 (3.42 g, 0.01 mol) in MeOH/MeCN 7:3 (100 ml) was electrolyzed at a current density of 0.05 A/cm^2 (cell voltage: 4.7 V) at r.t. under N_2[5]). After 4 F/mol electricity had passed, the mixture was poured into a 0.1N aq. H_2SO_4 soln. (100 ml) and extracted with Et_2O. Usual workup and distillation *in vacuo* gave **5a** (**5b**)/**2a** (**2b**) in a 65:35 ratio (0.011 mol). Anal. data (purification: column chromatography on silica gel, cyclohexane/AcOEt 95:5) were identical with those in [1][3].

5,5-Dimethoxycyclopentadec-1-yne (**7a**). Anodic oxidation (see above) of *bicyclo[10.3.0]pentadec-1(12)-ene-13-one* (**2a**) was performed using carefully dried solvents [8] and a new graphite anode. At the end of the electrolysis, the soln. was divided into two portions, one for product isolation and purification, and the other for the hydrolysis experiment (see below).

The solvents of the first crop were removed under reduced pressure, and the resulting viscous residue was triturated with dry Et_2O (100 ml) to precipitate the electrolyte. After filtration and concentration, the crude mixture was distilled *in vacuo* to give a first fraction (b.p. 70–120°) containing the methyl esters of *p*-toluenesulfinic and *p*-toluenesulfonic acid as major components and a higher-boiling mixture (b.p. 120–150°) **7a**/**2a** 2:1.

TsMe. ^1H-NMR: 2.44 (*s*, 3 H); 3.48 (*s*, 3 H); 7.35 (*d*, $J = 7.6$, 2 H); 7.60 (*d*, $J = 7.6$, 2 H). MS: 170 (55, $M^{+\cdot}$), 155 (3), 139 (100), 121 (5), 111 (11), 91 (43), 77 (19), 65 (28), 51 (7), 45 (6), 39 (12).

TsOMe. ^1H-NMR: 2.46 (*s*, 3 H); 3.75 (*s*, 3 H); 7.36 (*d*, $J = 7.8$, 2 H); 7.79 (*d*, $J = 7.8$, 2 H). MS: 186 (48, $M^{+\cdot}$), 155 (46), 139 (2), 122 (8), 107 (13), 91 (100), 79 (9), 65 (28), 51 (4), 39 (12).

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[3]) The mesylhydrazone of **2a** exhibited the same two-electrons irreversible oxidation wave at 1.2 V (*vs.* SCE) as did tosylhydrazone **6a**.

[4]) Quality *ELLOR 12*, purchased from *Le Carbone S.A.*, CH–3000 Bern.

[5]) Controlled-potential electrolyses at 1.2 V (*vs.* SCE) gave identical current efficiencies and product distributions.

Compound **7a** was identified in comparison with an authentic sample prepared separately as follows [9]: a mixture of *cyclopentadec-4-yn-1-one* (**5a**; 1 g, 4.5 mmol), methyl orthoformate (0.5 g, 4.5 mmol), MeOH (0.2 ml, 4.5 mmol), and conc. HCl (0.003 ml) was allowed to stand for 24 h at r.t. After neutralization with piperidine, the product was isolated by distillation (bulb-to-bulb: b.p. 130–140°/0.02 Torr). IR: 3010–2800, 1455, 1430, 1345, 1285, 1230, 1115, 1080, 1045. ^{1}H-NMR: 1.30–1.50 (br. *m*, 16 H); 1.70 (*m*, 2 H); 1.84 (*t*, $J = 6.5$, 2 H); 2.22 (br. *m*, 4 H); 3.12 (*s*, 6 H). MS: 266 (7, $M^{+\cdot}$), 235 (34), 191 (8), 177 (18), 163 (30), 149 (12), 137 (17), 123 (71), 109 (38), 101 (78), 88 (100), 79 (57), 67 (52), 55 (58), 41 (56).

Hydrolysis of **7a** *and* **2a**. Aq. H_2SO_4 (0.5 ml, 0.1%) was added to the second portion of the above crude electrolysis soln. under magnetic stirring at r.t. The quantitative conversion of **7a** into **5a** was followed by GLC, using the unreactive **2a** originally present as internal standard. The reaction was complete within 3.5 h.

TsOMe. Commercially available TsNa (1 g, 5.6 mmol) was added to a stirred soln. of Bu_4NClO_4 (1.7 g, 5 mmol) in MeOH/MeCN 7:3 (50 ml) in the electrolysis cell at r.t. Conc. H_2SO_4 (1 equiv.) was then added at once. After 15 min, no trace of ester having been detected, the electrolysis was started at a current density of 30 mA/cm^2, until 2 F/mol electricity based on the initial Na salt have passed. Continuous formation of the ester could be monitored by GLC from the beginning of the oxidation. Usual workup of the mixture and purification by distillation (bulb-to-bulb: b.p. 70–80°/0.01 Torr) gave 45% of TsOMe (0.42 g, 2.53 mmol).

Methanesulfonohydrazide [10]. To a stirred ice-cold soln. of hydrazine hydrate (2.5 g, 50 mmol) in H_2O (7.5 ml), MsCl (5.75 g, 50 mmoles) was added slowly, followed by 2N aq. NaOH (25 ml), so that the temp. did not exceed +8°. At the end of the additions, the mixture was evaporated under reduced pressure, and the oily residue was treated with Et_2O. NaCl was filtered off and the solvent evaporated. A colourless oil (5 g, 45 mmol), which crystallized slowly on standing (m.p. 49°), was obtained in 90% yield. IR: 3340, 3240, 3000–2910, 1610, 1390, 1320, 1145, 1035, 965. ^{1}H- NMR: 3.00 (*s*, 3 H); 5.45 (br. *s*, 1 H, exchangeable with D_2O). MS: 110 (6, $M^{+\cdot}$), 95 (100), 80 (36), 65 (76), 63 (48), 61 (6), 55 (4), 46 (20), 43 (22).

Methanesulfonylhydrazone of **2a**. A soln. of **2a** (1.7 g, 7.9 mmol) and methanesulfonohydrazide (1 g, 9 mmol) in 95% EtOH (10 ml) was refluxed for 7 h. The hydrazone crystallized on cooling. Filtration and recrystallization from EtOH afforded 1.5 g (4.8 mmol, 61%) of pure **2a**. M.p. 176–177°. IR: 3200, 3000, 2910, 1615, 1395, 1305, 1165, 960. ^{1}H- NMR: 1.14–1.70 (*m*, 16 H); 2.33 (*m*, 4 H); 2.43 (*m*, 2 H); 2.51 (*m*, 2 H); 3.11 (*s*, 3 H); 6.82 (br. *s*, 1 H, exchangeable with D_2O). MS: 312 (4, $M^{+\cdot}$), 233 (100), 216 (7), 204 (4), 177 (4), 161 (4), 147 (11), 133 (16), 120 (17), 105 (26), 91 (72), 79 (94), 65 (31), 55 (42), 41 (75).

Anodic Oxidation of the Methanesulfonylhydrazone of **2a**. Electrolysis of the methanesulfonylhydrazone derivative of **2a** (3.1 g, 10 mmol) following the *General Procedure* generated, after purification by distillation, a mixture (1.34 g, 6.1 mmol; 61% combined yield) **5a**/**2a** 23:77.

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